Remarks/Arguments:

Claims 15-38, presented hereby, are pending.

Claims 8-14 are cancelled, hereby, without prejudice or disclaimer.

The specification is amended, hereby, by identifying sequences in specification with the corresponding identification number found in the Sequence Listing. Additionally, corrections are made to page 27 of the specification, to be consistent with disclosure at specification pages 6-8, i.e., in connection with sequence identified in the Sequence Listing as SEQ ID NO: 40.

Independent claims 15-18 contain subject matter originating from claim 8. Dependent claims 19-38 represent the subject matter in claims 9, 10, and 12-14, made dependent on each of the independent claims.

For easy understanding and clear definition of the invention, Applicants divided the subject matter included in claim 8 into four embodiments, each of which corresponds to one of claims 15-18.

The methods of claims 15 and 16 use PaSS (Pattern Similarity Score), but the methods of claims 17 and 18 use genome semi-distance, represented by the formula (1-Pass)/Pass, in place of PaSS. In claim 8, both parameters are utilized in parallel and make the invention slightly complicated.

In addition, the method of claims 15 and 16 is limited to a method for determining the similarity at the genome level between a target organism and a reference organism. On the other hand, the method of claim 17 and 18 is directed to a method for identifying a reference organism closest at the genome level to a target organism.

In the method of claim 15, only one specific organism is used as a reference organism and the reference organism is not altered with the others and by this method, and it is possible to determine that whether or not a target organism is the same organism as the reference organism. If the value of PaSS is 1, it is concluded that the target organism is the same organism as the reference organism. In addition, it is also possible to determine, even if the value of PaSS is not 1, that the target organism has high or low similarity with the reference organism from the PaSS value. PaSS value of a target organism having high similarity with a reference organism is close to 1 and PaSS value of a target organism having low similarity with a reference organism is far from 1.

In the method of claim 16, calculation of PaSS of step e) is repeated in step f) with altering the reference organism registered in a database until the maximum PaSS is obtained. By this process, the closest reference organism at the genome level to the target organism can be identified. If the closest reference organism is identified, the species of a target organism will be presumed and if PaSS between the target organism and the closest reference organism is 1, the species of the target organism can be determined as the same species as that of the closest reference organism.

Support and details for the subject matter in claims 15-18 are as follows.

Items (1) - (5), below, are common to claims 15-18.

(1) The term "featuring point"

Applicants replaced the term "featuring point" with "the melting initiation point and/or the mobility transition end point" in claims 15 and 16. The featuring points are a generic term and includes "the melting initiation point and/or the mobility transition point" as mentioned in page 17

lines 2 to 10. In this paragraph, the mobility transition end point is referred to "mobility end point" but it would be more adequate to donate the point as "mobility transition end point". This is because the phenomena caused at the melting point are termination of denaturation of a double-stranded DNA to a single-stranded state. In this connection, please refer to page 17 line 11 from the bottom to page 18, line 3.

(2) Step b); co-migration of reference DNA

Applicants use the term "internal reference double-stranded DNA" in place of a double-stranded standard DNA fragment as an internal reference". Further, it is defined in step b) that the internal reference DNA should be one of which the melting initiation point and the mobility transition end point are determinen. In addition, Applicants clarify in step b) that the internal reference double-stranded DNA prepared in advanced is co-migrated with the double-stranded DNA fragments of the target organism.

This means that the internal reference double-stranded DNA should be one exhibiting the melting initiation point and the mobility transition end point, and different from the DNA fragments of target organism. In this invention, examples of the internal reference double-stranded DNA are selected from DNA fragments with clear melting initiation point and mobility transition point.

With respect to the "internal reference double-stranded DNA", Applicants have the following support in the specification on page 10, lines 13 to 22.

The pseudo-absolute position of the identification dot of each double-stranded DNA can be determined from the locational relation to the electrophoresis pattern of the standard DNA. The

standard DNA can be a kind of an inner standard specimen. Using such standard DNA allows analyzing data, which are obtained by the electrophoresis and have deviation to some extent depending on the condition, based on the same standard. Namely, using standard DNA allows correcting data which are obtained from electrophoresis pattern and normalizing them.

(3) Step c)

Due to change of step b), step c) was changed accordingly.

(4) Step d)

With the use of the internal reference double-stranded DNA, it is possible to subject the melting initiation point and/or the mobility transition end point of double-stranded DNA fragments of the target organism to normalization of coordinate for generation of species identification dots. These procedures enable elimination of experimental fluctuation.

In the description on page 10, lines 13 to 22, the internal reference double-stranded DNA is described to be used for such normalization.

(5) Step e)

Calculation of PaSS from species identification dots obtained in Step d) using equations (1) and (2) is described on page 20, lines 18 to 21, line 4 from the bottom.

(6) Step f) in claim 16

Attention is directed to page 22, line 5 from the bottom, to page 23, line 5 of the instant specification. It is mentioned that comparison with other reference genome (in a database) is repeated until a PaSS value goes over a standard value.

In practice, the database is provided on the web site and a researcher contacts the web site database and conducts repeated calculation to obtain the results. In addition, the database will be supplemented by researchers utilizing this database for abundance of the data.

Claims 8-14 were rejected under 35 USC 112, ¶2, for a allegedly being indefinite. Reconsideration is requested in view of the changes reflected in new claims 15-18, discussed above, and as further discussed below.

Applicants submit that the rejection is overcome by the new claims, in particularly, because:

- the present claims are written in a clear, stepwise manner;
- featuring points are amended to use the more specific terms "the melting imitation point and/or the mobility transition end point"; and
- the meaning of the internal reference sample is clarified.

The term "material" (claim 11) is not found in the present claims. The term is replaced with the term "primer or nucleotide," by incorporating the subject matter of claim 12 into claim 11, e.g., as found in present claim 21

Claims 8, 10, 13, and 14, were rejected under 35 USC 103(a) for allegedly having been obvious based on 'Nishigaki-A" in view of "Nishigaki-B" and 'Nishigaki-C." Claim 9 was rejected under 35 USC 103(a) for allegedly having been obvious based on 'Nishigaki-A" in view of 'Nishigaki-B," "Nishigaki-C," as applied above, and further in view of GenBank accession numbers J02448 and AE00017. Claims 11 and 12 were rejected under 35 USC 103(a) for allegedly having

been obvious based on "Nishigaki-A" in view of "Nishigaki-B," "Nishigaki-C," as applied above, and further in view of Pena. Reconsideration of the aforesaid rejections under §103(a) is requested.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). A "ground of rejection is simply inadequate on its face . . . [when] the cited references do not support each limitation of [the] claim." *In re Thrift*, 63 USPQ2d 2002, 2008 (Fed. Cir. 2002). When conducting an obviousness analysis, "all limitations of a claim must be considered in determining the claimed subject matter as is referred to in 35 U.S.C. 103 and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982).

Comparison of claim 15 to the references

Nishigaki-A

The PTO sets forth in the Official Action that the limitations of claim 8, steps (a) and (b) are identical to that of the method taught by Nishigaki-A.

In accordance with the present claims, step (b) use of the internal reference double-stranded DNA, of which the melting initiation point and the mobility transition end point are determined, is required. On the other hand, the use of such DNA is not taught or suggested by Nishigaki-A.

In addition, although the PTO states that the purpose of the instant invention is to identify a characterized piece of genomic DNA, the actual purpose of the presently claimed invention is to provide a method of determination of the similarity at the genome level between a target organism and a reference organism.

The PTO recognized that internal references are co-migrated double stranded DNAs as demonstrated in figure 3(a-c) labeled A, B, and C. However, the co-migrated double stranded DNAs labeled A, B, and C are corresponding double stranded DNAs of single stranded DNAs labeled A', B' and C' and it can be said that they are double stranded DNAs of a target organisms. Therefore, the co-migrated double stranded DNAs are different from the internal reference double-stranded DNA used in the present invention.

As mentioned above, the internal reference double-stranded DNA used in the present invention is that of which the melting initiation point and the mobility transition end point are determined and is able to use for normalization of the melting initiation point and/or the mobility transition end point of a double-stranded DNAs of a target organism.

In contrast, the melting initiation point and the mobility transition end point are not determined with respect to the double stranded DNAs labeled A, B, and C in Nishigaki-A and therefore, the double stranded DNAs labeled A, B and C can not be used for normalization.

Due to lack of descriptions with respect to the internal reference double-stranded DNA, it is as a matter of course that Nishigaki-A fails to teach (i) normalization of coordinates of the melting points and/or the mobility transition end points using those of the internal reference double-stranded

DNA, (ii) calculation of PaSS utilizing species identification dots generated by the normalization and (iii) determination of the similarity at the genome level between a target organism and a reference organism by the resultant PaSS value.

Nishigaki-B and C

At first, please note that the reference cited on the first and fourth lines of the paragraph 3 of page 6 of the Office Action. "Nishigaki-B" should be "Nishigaki-C". Nishigaki-B does not have page 151.

Since the PTO confused Nishigaki-B and Nishigaki-C in the Official Action, it renders uncertain the PTO's comments.

The PTO states that it would have been obvious for one of ordinary skill in the art to perform the base method taught by Nishigaki-A and improve the generic analysis of the mobility transition profile analysis as per the teachings of Nishigaki-B and Nishigaki-C.

However, Nishigaki-B and Nishigaki-C fail to teach co-migration of the internal reference double-stranded DNA as well as (i) to (iii) pointed out above, which are not taught by Nishigaki-A.

That is, Nishigaki-B and Nishigaki-C are silent about (i) normalization of coordinates of the melting initiation points and/or the mobility transition end points using those of the internal reference double-stranded DNA, (ii) calculation of PaSS utilizing species identification dots generated by the normalization and (iii) determination of the similarity at the genome level between a target organism and a reference organism by the resultant PaSS value.

In the method of Nishigaki-B, a dye is used for cancellation of mobility shifts caused by experimental fluctuations by normalizing the mobility of sample with respect to the corresponding one of the day. However, the dye does not exhibit the melting initiation point and the mobility transition end point, and is totally different from the internal reference double-stranded DNA used in the present invention.

In addition, the samples utilized in Nishigaki-B are oligonucleotides and in general, oligonucleotides do not exhibit the melting initiation point and the mobility transition end point. In the figures shown in Nishigaki-B, no oligonucleotide exhibits the melting initiation point and the mobility transition end point.

A mobility profile of a double stranded DNA dealt in Nishigaki-C was processed to bear a differential curve containing peaks and troughs (see Nishigaki-C Fig. 7). However, these peaks and troughs, which are in a sense featuring, can not serve as featuring points called as species identification dots (spiddos) for the claimed technology due to the following reasons:

(i) The differential curve (and its original curve) was obtained after several laborious steps such as digitizing of a migration band pattern of DNA by manually tracing it on a digitizer tablet as well as that of a dye migration pattern (Nishigaki-C, p. 145 "data conversion"); those data input into the computer were processed to generate a normalized band pattern of dsDNA using the reference band pattern of a dye by computer; and then the normalized band pattern (a curve) was differentiated by computer to provide the final differential curve, as can be seen in Fig. 7c. (On the

other hand, spiddos can be obtained directly from a GP image without any data processing owing to its practical definition.)

(ii) The number of the maximum or minimum points extracted from a differential curve as in Fig. 7 varies from sequence to sequence and can not be uniquely defined, which is a fatally unfavorable nature for the current purpose.

(iii) Those points said in (ii) are determined to be unstable and less reproducible (which was found by the inventors after a long term accumulation of experimental data and first publicized in Genome Biology (2002)), which is also crucially unfavorable for the current purpose, since Applicants can not make such unstable points for the reference points required for normalization.

On the other hand, the melting initial point is determined to be very unique, stable and reproducible (also publicized in Genome Biology (2002); see page 6 "Extraction of Spiddos"). Evidently, this finding required around 10 years incessant endeavor of the inventors. Therefore, it is by no means prima facie obvious to select appropriate dsDNAs (not a dye nor oligonucleotide), select the melting initial point as a standard point for the current purpose, and think of using it for comparison of species, as is shown by the fact that no one else has ever found this technology independently until now, despite the fact that the references of Nishigaki-A, -B, and -C had been published more than 10 years ago. (Especially it is obvious that nobody else could find the value of this technology ever since)

The PTO states in the Official Action that "yet the process of selecting featuring points from the images are described in greater detail in the incorporated reference (Nishigaki-C) but Nishigaki-C completely fails to teach selection of the melting initiation point and the mobility transition end point, as mentioned in detail above.

Even though the method of Nishigaki-A is combined with the modification of Nishigaki-B and Nishigaki-C, claim 15 would not be completed. This is because Nishigaki-B and Nishigaki-C do not teach the defects of the method of Nishigaki-A.

Comparison of claims 16-18 with references

The above arguments with respect to claim 15 are equally applicable to claims 16-18. In addition, none of the references teaches that calculation of PaSS of step e) is repeated with altering the reference organism until the maximum PaSS is reached in order to identify a reference organism closest at the genome level to a target organism. Thus, even though the method of Nishigaki-A is combined with the modification of Nishigaki-B and Nishigaki-C, claim 16 would not be completed because Nishigaki-B and Nishigaki-C do not teach the defects of the method of Nishigaki-A.

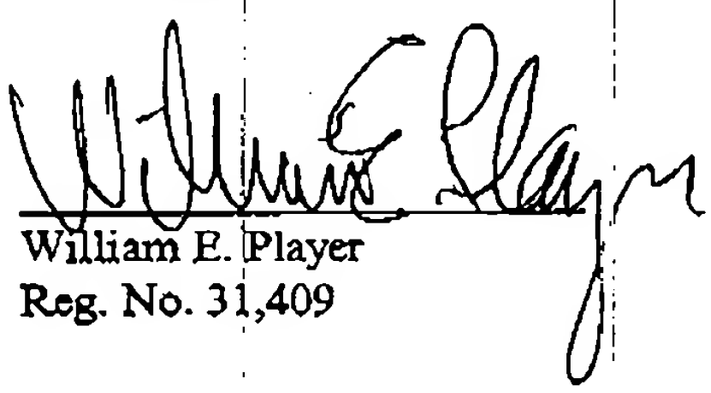
As explained, above, all of the features (limitations) in each of claims 15-18 are neither taught nor suggested by the cited references and, so, the rejections of record under §103(a) cannot be maintained. *Royka, supra.* Since "the cited references do not support each limitation of [the] claim[s]," the §103(a) rejection is "inadequate on its face," *Thrift*, 63 USPQ2d at 2018. Dependent claims 19-38 are patentable over the cited references under §103(a), by virtue of being dependent

on one of claims 15-18. If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By 

William E. Player
Reg. No. 31,409

400 Seventh Street, NW
The Jenifer Building
Washington, D.C. 20004
Tel. (202) 638-6666
Fax (202) 393-5350
Date: December 1, 2003
WEP/bap
R:\Home\RTHOMAS\2003\OCTOBER\P66602US0 amd.wpd